Remarks/Arguments

Claims 22-32 are pending in the subject application. Claims 22, 25 and 28 were amended to more accurately define the method as a method for diagnosing a renal disease or condition with renal complications. Support for this amendment is found throughout the specification and original claims, where several conditions and diseases are listed. Claim 28 was further amended to correct typographical errors, delete "subjective" terms, *i.e.*, "extensive" and "drug abuse," and provide meaning for two acronyms used therein. The dependency of claim 29 was corrected; and typographical errors in claim 32 were corrected.

The specification was amended to provide updated priority information.

No new matter is added by the amendments to the specification and claims.

I. Claim Objections

It is respectfully submitted that the amendments to the claims render the objections to the claims listed on page 2 of the Office Action moot.

II. Rejection of Claim 28 Under 35 U.S.C. § 112, Second Paragraph

It is respectfully submitted that the amendments to claim 28 render this rejection moot.

III. Rejection of Claims 22-32 Under 35 U.S.C. § 112 (Written Description)

The Examiner states that the specification fails to provide written description of the claimed method because there is no description of distinguishing identifying characteristics of the protein fragmentation profiles for specific diseases and/or conditions.

This rejection is respectfully traversed as follows.

The present invention is based, in part, on applicant's discovery that in renal disease or conditions that affect renal function, fragmentation of excreted proteins by renal passage is inhibited. Proteins are heavily degraded during renal passage in normal, healthy individuals and the breakdown products are excreted in the urine. The urine of an individual with normal functioning kidneys, *e.g.*, a person who does not have kidney disease or a condition that presents with renal complications, contains proteins that are excreted as a mixture of some native protein (full length) and primarily fragmented protein. Figures 5, 6 and 7 of the specification provide typical fragmentation profiles obtained by HPLC of urinary albumin of a normal, healthy individual.

In contrast, the HPLC-derived urinary albumin profiles of individuals whose kidneys are not functioning properly show a decreased amount of smaller fragments and a shift toward larger fragments and an increasing amount of substantially full length albumin, followed later in time by an increasing amount of native protein. This is demonstrated in Figures 3 and 4. Figure 3 is a fragmentation profile created by size exclusion chromatography of urinary protein from a normal, healthy individual. This figure shows a fragmented albumin peak, but no full length albumin , In contrast, the fragmentation profile of urine from a diabetic patient (Figure 4) shows both intact and fragmented albumin.

Figure 7 is an HPLC generated fragmentation profile of urine from a healthy individual, which shows only fragmented albumin, but no full length albumin. In contrast, Figure 8, which is the HPLC fragmentation profile of urine from a normal buminuric diabetic patient shows an intact albumin peak in addition to the smaller fragments seen in the profile of normal individuals.

The data shown in these figures demonstrate a trend that applies to all individuals with renal dysfunction. That is, there is a shift on the protein fragmentation profile from protein fragments

toward an increasing amount of substantially full length protein, and less fragmentation, indicating that the kidneys are not functioning normally to fragment filtered proteins.

The examiner states at page 4 of the Office Action that the specification does not demonstrate any structural or functional characteristics of the proteins that are used to detect the disease/condition. This is incorrect. The specification, and Figures cited above, clearly demonstrate that in healthy individuals, protein, *e.g.*, albumin is almost all fragmented, whereas in the profiles of individuals afflicted with renal dysfunction, the size of urinary protein fragments is shifted to larger fragments and the amount of substantially full length protein is significantly increased.
Moreover, the same is true of all proteins. During renal filtration proteins are degraded, not randomly, but on the basis of their structure. Thus, each protein is degraded in a pattern determined by its structure. However, in a diseased individual, the mechanism by which cutting is carried out does not work properly, resulting in less cutting and larger fragments.

The protein fragmentation profiles of diseased individuals show an increased proportion of larger fragments and substantially full length protein and a significant decrease in amount of small fragments. As the specification discloses, the comparison of healthy versus diseased fragmentation profiles is one of amount of fragments/full length protein or amount of small fragments versus large fragments. The comparison shows a shift to larger fragments and substantially full length protein, which is readily detected. Thus, the specification provides sufficient written description of the characteristics of the protein profiles to distinguish healthy individuals from those with renal disease/conditions.

Moreover, it is the relative health of the kidneys that affects protein fragmentation, rather than the specific disease responsible for the kidney dysfunction. Thus, the protein fragmentation profiles caused by any of the conditions listed in claim 28 is a reflection on how well the kidneys are functioning to filter and fractionate protein, rather than a function of the specific disease state. The specification discloses several albumin fragment profiles of healthy individuals as well as for individuals with renal dysfunction. These fragmentation profiles demonstrate a trend that is seen with renal dysfunction that affects fragmentation of filtered proteins. That is, there is a shift from smaller fragments towards substantially larger fragments or full length protein in the urine, regardless of the particular protein or disease state being analyzed.

Furthermore, it is irrelevant which urinary protein is analyzed since the kidneys filter and fragment all proteins indiscriminantly. Thus, a fragmentation profile from healthy individuals can be obtained for any protein and used as a reference for the protein fragmentation profile obtained from a diseased individual. The application of the claimed diagnostic method is the same regardless of the protein being analyzed. That is, the fragmentation profiles of healthy versus diseased individuals is analyzed for a shift toward inhibition of fragmentation, which is observed as a relative increase in the amount of substantially full length protein. The specification discloses this and provides examples of such.

As such, there specification provides sufficient written description to satisfy the requirements of 35 U.S.C. § 112, first paragraph. Accordingly, the rejection of claims 22-32 under 35 U.S.C. § 112, first paragraph is respectfully traversed.

IV. Rejection of Claims 22-32 Under 35 U.S.C. § 112 (Enablement)

Claims 22-32 stand rejected under 35 U.S.C. § 112, first paragraph. The examiner states that the specification does not enable one of skill in the art to make or use the claimed invention

because the specification does not describe the protein fragmentation profiles for each of the various diseases.

This rejection is respectfully traversed as follows.

As discussed above, the particular disease responsible for the kidney dysfunction does not determine the protein fragmentation profile for an individual. Rather, the ability of the kidneys to filter and fragment protein is the driving force behind the protein profile. Thus, regardless of the cause, there is a trend toward larger fragments and substantially full length protein in urine obtained from individuals with renal dysfunction as opposed to the smaller fragmentation of proteins and relative absence of full length protein observed in urine of healthy individuals.

The specification teaches how to obtain protein fragmentation profiles from both healthy and diseased individuals. The specification also provides examples of profiles from healthy and diseased individuals. A trend toward less fragmentation and more larger fragments, and more substantially full length protein in the urine of diseased individuals is disclosed and shown in the figures. Thus, on the basis of the teachings of the present specification one of skill in the art would be able to obtain and analyze the fragmentation profile of any individual and make a determination as to whether the profile shows a shift from normal to that of a diseased state indicative of renal dysfunction. As such, the present specification enables the claimed invention.

Accordingly, the rejection of claims 22-32 under 35 U.S.C. § 112, first paragraph is respectfully traversed.

It is respectfully submitted that the present application is in condition for allowance, an early notification thereof being earnestly solicited.

To the extent necessary, a petition for an extension of time under 37 C.F.R. 1.136 is hereby made. Please charge any shortage in fees due in connection with the filing of this paper, including extension of time fees, to Deposit Account 500417 and please credit any excess fees to such deposit account.

Respectfully submitted,

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